statistics, see for example the homepage for the American Heart Association at http://www.amhrt.org/1997/ stats/Stroke.html]

A second model (Jiang et al. (1995) *Stroke* 26:1-40), utilized mature Wistar rats [rates] which underwent temporary occlusion of the middle cerebral artery by intra-arterial suture for two hours. At the time of reperfusion either bFGF (45 μg/kg/hr) or vehicle were infused intravenously over three hours. At seven days after ischemia, infarct volume was significantly reduced in the bFGF treated animals (approximately 40% reduction in infarct volume), and only the bFGF treated animals regained their weight after surgery.

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

1. (Amended) A method for limiting damage to neuronal cells by ischemic or hypoxic conditions, comprising administering to an individual a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in amounts effective for reducing cerebral infarct volume relative to the absence of administration of the *ptc* therapeutic and the *hedgehog* polypeptide, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP.

2. (Amended) A method for protecting cerebral tissue of a mammal against the repercussions of ischemia which comprises administering to the mammal in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP.

3. (Amended) A method for the treatment of cerebral infarctions which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in therapeutically effective amounts,

wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP.

4. (Amended) A method for the treatment of cerebral ischemia which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP.

5. (Amended) A method for the treatment of stroke which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP.

6. (Amended) A method for the treatment of transient ischemia attack which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP.

7. (Reiterated) The method of any of claims 1-6, wherein the *ptc* therapeutic binds to *patched* and mimics *hedgehog*-mediated *patched* signal transduction.

8. (Amended) The method of claim 7, wherein the *ptc* therapeutic is a small organic molecule having a molecular weight less than 5 kD.

9. (Reiterated) The method of claim 7, wherein the binding of the *ptc* therapeutic to *patched* results in upregulation of *patched* and/or *gli* expression.

10. (Reiterated) The method of claim 8, wherein the *ptc* therapeutic is a small organic molecule which interacts with neuronal cells to mimic *hedgehog*-mediated *patched* signal transduction.

11. (Reiterated) The method of any of claims 1-6, wherein the *ptc* therapeutic mimics *hedgehog*-mediated *patched* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in a *patched* signal pathway.

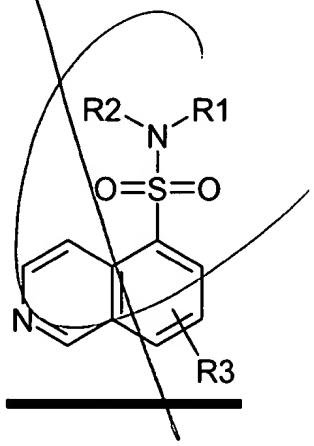
12. (Reiterated) The method of any of claims 1-6, wherein the *ptc* therapeutic alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in the intracellular signal transduction pathway of *patched*.

13. (Amended) The method of claim 11, wherein the *ptc* therapeutic is a small organic molecule having a molecular weight less than 5 kD which binds to *patched* and regulates *patched*-dependent gene expression.

14. (Reiterated) The method of claim 11, wherein the *ptc* therapeutic is an inhibitor of protein kinase A (PKA).

15. (Reiterated) The method of claim 14, wherein the PKA inhibitor is a 5-isoquinolinesulfonamide.

16. (Amended) The method of claim 15, wherein the PKA inhibitor is represented in the general formula:



wherein, as valence permits,

R_1 and R_2 each independently represent hydrogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$, or

R_1 and R_2 taken together with N form a substituted or unsubstituted heterocycle;

R_3 is absent or represents one or more substitutions to the isoquinoline ring such as a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$;

R_8 represents a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; and

n and m are independently for each occurrence zero or an integer in the range of 1 to 6.

17. (Reiterated) The method of claim 14, wherein the PKA inhibitor is selected from the group consisting of N-[2-((p-bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, KT5720, and PKA Heat Stable Inhibitor isoform α.

18. (Reiterated) The method of claim 5, wherein the stroke is a thrombotic stroke.

19. (Reiterated) The method of claim 5, wherein the stroke is an embolic stroke.

20. (Reiterated) The method of claim 1, wherein the conditions result in cerebral hypoxia.

21. (Reiterated) The method of claim 1, wherein the conditions result in progressive loss of neurons due to oxygen deprivation.

22. (Reiterated) The method of any of claims 3-6, wherein the patient is treated prophylactically.

23. (Reiterated) The method of claim 1, wherein the individual is treated prophylactically.

24. (Reiterated) The method of claim 2, wherein the mammal is treated prophylactically.

a1 25. (Amended) The method of claim 1, wherein the individual is hypotensive.

26. (Reiterated) The method of any of claims 1-6, further comprising administering one or more of an anticoagulant, an antiplatelet agent, a thrombin inhibitor, and/or a thrombolytic agent.

27. (Reiterated) The method of any of claims 1-6, further comprising performing vascular surgery.

28. (Reiterated) The method of claim 27, wherein the vascular surgery comprises carotid endarterectomy.

29. (Reiterated) The method of any of claims 1-6, wherein treatment of the patient with the *ptc* therapeutic results in at least a 25% reduction in cerebral infarct volumes relative to absence of treatment with the *ptc* therapeutic.

30. (Reiterated) The method of claim 29, wherein treatment of the patient with the *ptc* therapeutic results in at least a 50% reduction in cerebral infarct volumes relative to absence of treatment with the *ptc* therapeutic.

31. (Reiterated) The method of claim 29, wherein treatment of the patient with the *ptc* therapeutic results in at least a 70% reduction in cerebral infarct volumes relative to absence of treatment with the *ptc* therapeutic.

32. (Reiterated) The method of any of claims 1-6, wherein the *ptc* therapeutic inhibits the activity of PKA, cAMP, or adenylate cyclase.

33. (Amended) The method of any of claims 1-6, wherein the *ptc* therapeutic agonizes the activity of cAMP phosphodiesterase.

34. (Amended) A therapeutic preparation comprising a *hedgehog* polypeptide and a small molecule antagonist of *patched*, provided in a pharmaceutically acceptable carrier and in amounts sufficient to provide protection against neuronal cell death under ischemic and/or hypoxic conditions.

35. (Reiterated) The preparation of claim 34, which *patched* antagonist binds to *patched*.

36. (Reiterated) The preparation of claim 34, wherein the *patched* antagonist is provided in an amount sufficient to produce, upon a dosage regimen of 7 days, at least a 70% decrease in infarct volume in an MCAO model relative to the absence of the *patched* antagonist.

37. (Reiterated) The preparation of claim 34, wherein the *patched* antagonist is provided in an amount sufficient to produce, upon a dosage regimen of 3 days, at least a 70% decrease in infarct volume in an MCAO model relative to the absence of the *patched* antagonist.

The amendments presented above incorporate changes as indicated by the marked-up versions below.

1. (Amended) A method for limiting damage to neuronal cells by ischemic or [epoxic] hypoxic conditions, comprising administering to an individual a therapeutic regimen including administering a *hedgehog* polypeptide and administering a *ptc* therapeutic in [an] amounts effective for reducing cerebral infarct volume relative to the absence of administration of the *ptc* therapeutic and the *hedgehog* polypeptide, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP [inhibits PKC with a K_i greater than 1 μM, whereby damage to neuronal cells is limited by the administration of the *ptc* therapeutic].

2. (Amended) A method for protecting cerebral tissue of a mammal against the repercussions of ischemia which comprises administering to the mammal in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide [a therapeutically effective amount of] and administering a *ptc* [therapeutic] therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP [inhibits PKC with a K_i greater than 1 μM].

3. (Amended) A method for the treatment of cerebral infarctions which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide [a therapeutically effective amount of] and administering a *ptc* [therapeutic] therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP [inhibits PKC with a K_i greater than 1 μM].

4. (Amended) A method for the treatment of cerebral ischemia which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide [a therapeutically effective amount of] and administering a *ptc* [therapeutic] therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP [inhibits PKC with a K_i greater than 1 μM].

5. (Amended) A method for the treatment of stroke which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide [a therapeutically effective amount of] and administering a *ptc* [therapeutic] therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP [inhibits PKC with a K_i greater than 1 μM].

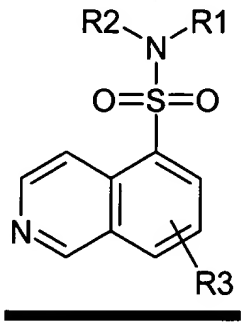
6. (Amended) A method for the treatment of transient ischemia attack which comprises administering to a patient in need thereof a therapeutic regimen including administering a *hedgehog* polypeptide [a therapeutically effective amount of] and administering a *ptc*

[therapeutic] therapeutic in therapeutically effective amounts, wherein the *ptc* therapeutic is a PKA inhibitor, a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase, or an antagonist of cAMP [inhibits PKC with a K_i greater than 1 μM].

8. (Amended) The method of claim 7, wherein the *ptc* therapeutic is a small organic molecule having a molecular weight less than 5 kD.

13. (Amended) The method of claim 11, wherein the *ptc* therapeutic is a small organic molecule having a molecular weight less than 5 kD which binds to *patched* and regulates *patched*-dependent gene expression.

16. (Amended) The method of claim 15, wherein the PKA inhibitor is represented in the general formula:



wherein, as valence permits,

R_1 and R_2 each [can] independently represent hydrogen, [and as valence and stability permit] a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n$-O-$(CH_2)_m-R_8$, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n$-S-$(CH_2)_m-R_8$, or

R_1 and R_2 taken together with N form a substituted or unsubstituted heterocycle;

R_3 is absent or represents one or more substitutions to the isoquinoline ring such as a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl [(such as a carboxyl, an ester, a formate, or a ketone)], a thiocarbonyl [(such as a thioester, a thioacetate, or a thioformate)], an